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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,278	05/24/2001	Pieter Jacob Swart	702-002214	9397

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EXAMINER	
TELLER, ROY R	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,278	SWART ET AL.	
	Examiner	Art Unit	
	Roy Teller	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-15,22 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-15, 22, 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment, received 9/8/06. Applicant has amended claims 1 and 8. New claim 40 has been added.

Claims 1, 4-15, 22 and 40 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 40 is/ stands rejected under 35 USC 112, first paragraph for the reasons of record which are restated below.

Claim 40 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for bovine lactoferrin and fluconazole for the treatment of *Candida* does not reasonably provide enablement for a medicament for treatment and/or preventment of infections and/ or inflammation caused by Candida species, selected from the group of polypeptides or derivatives thereof, listed in claim 40. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the breadth of the claims;
3) the predictability or unpredictability of the art
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The claimed invention is drawn to a medicament for treatment and/or prevention of infections and/or inflammation caused by Candida species, said medicament comprising an active amount of a polycationic peptide or protein, and a buffer for maintaining the pH of treatable tissue within a preselected range, selected from the group of polypeptides or derivatives therof, listed in claim 40 .

The breadth of the claims is excessive with regard to claiming medicament for treatment and/or preventment of infections caused by Candida species, said medicament comprising an active amount of a polycationic peptide or protein, and a buffer for maintaining the pH of treatable tissue within a preselected range. Applicant has only provided guidance for the use of bovine lactoferrin and fluconazole for the treatment of *Candida*. Applicant have provided no guidance of any other medicament for treatment and/or preventment of infections caused by Candida species, said medicament comprising an active amount of a polycationic peptide or protein, and a buffer for maintaining the pH of treatable tissue within a preselected range, selected from the group of polypeptides or derivatives thereof, listed in claim 40 .

In absence of evidence to the contrary, it would not be expected that any

and all polycationic peptides or proteins would act as a medicinal agent . Furthermore, it would not be predictable to the artisan which polycationic peptides or proteins would work in the present invention, nor would it be predictable to the artisan which pathologies could be treated with these polycationic peptides or proteins.

Berendsen (Voet, Biochemistry, 2nd edition, 1995, pp-235-241) states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology and one of the most demanding challenges in the new field of bioinformatics." (Page 642). Berendsen states that, :Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the lowest free energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field. (Page 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). Voet[1] teaches that the mutant hemoglobin HbE [Glu B8(26)β → Lys] has, "no clinical manifestations in either heterozygotes or homozygotes." (Page 235). Further, Hb Boston and Hb Milwukee both have single point mutations which result in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state. Conversely, a single point mutation in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme

[1] D Voet and JG Voet. Biochemistry, 2nd Edition.(1995). 235-241.

center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state). (Page 236).

HbS is a single point mutation, Val → Glu A3(6)β (Page 236), which results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduely burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties.

In consideration of these factors, it is apparent that there is undue experimentation because of a variability in prediction of outcome that is not addressed by the present application. Absent factual data to the contrary, the amount and level of experimentation needed is undue to practice the invention as claimed.

Applicant's arguments were carefully considered but were not found persuasive.

Applicant contends that the specification provides more than adequate enablement for Claim 40. However, the examiner contends that the instant specification has only provided guidance for the use of bovine lactoferrin and fluconazole for the treatment of *Candida.* Guidance is not provided for derivatives thereof, nor prevention of infections and/or inflammation caused by *Candida*, using derivatives thereof.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-15 and 22 are stand rejected under 35 USC 103(a) for the reasons of record which are restated below.

Claims 1, 4-15 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wakabayashi et al (Antimicrobial agents and chemotherapy, 1998, vol. 42, no. 7, pp.-1587-1591) in view of Steinberg (WO 97/18827).

The claimed invention is drawn to a medicament for treatment and/or preventment of infections caused by Candida species, said medicament comprising an active amount of a polycationic peptide or protein, and a buffer for maintaining the pH of treatable tissue within a preselected range.

Wakabayashi beneficially teaches the effects of bovine lactoferrin (LF) coupled with fluconazole to inhibit hyphal growth of *Candida albicans* (see, e.g., for example, abstract, pp-1587 and pp-1589-1590). Wakabayashi does not teach a buffer for maintaining the pH of treatable tissue within a preselected range.

Steinberg beneficially teaches compositions suitable for treating oral mucositis with antimicrobial peptides comprising a polycationic peptide (lactoferrin) and a buffer which discloses a final pH value of 7.0-7.2 (see, e.g., for example, page 5, lines 23-34, page 26, lines 9-10, page 37, lines 8-22, page 38, lines 18-22, and page 62, claim 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have combined the teaching of Wakabayashi effects of bovine lactoferrin (LF) coupled with fluconazole inhibit hyphal growth of *candida albicans* with the beneficial teachings of Steinberg, because Wakabayashi discloses the therapeutic effects of lactoferrin related compounds against candidiasis due to *C. albicans* are being assessed.

Applicant's arguments were carefully considered but were not found persuasive.

Applicant contends that Wakabayashi teaches away from the claimed invention because Wakabayashi et al. teach the combination of lactoferrin with triazole antifungal agents. Applicants argue that the prior art discloses that "the peptide alone had almost no effect". However, the examiner contends that many investigators have reported on the anti-*Candida* activities of lactoferrin (LF). Lactoferrin B (Lfcin B) derived from bovine LF, exhibits potent disruptive effects on the fungal cell membrane and has fungicidal activity against *C. albicans*. See, i.e., for example, page 1587, 2nd column.

Conclusion

All claims are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy Teller whose telephone number is 571-272-0971. The examiner can normally be reached on Monday-Friday from 5:30 am to 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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ANISH GUPTA
PRIMARY EXAMINER